The Economic Impact of Cancer in Texas

Part 2: Literature Review and Analysis on Cancer Prevention and Cost-Effectiveness

Report to the Texas Comprehensive Cancer Control Coalition
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Introduction

Cancer is a group of related diseases that involve uncontrolled growth and spread of abnormal cells. In Texas in 1998, 32,275 people died from cancer. Of these cancer deaths, 9,513 were attributed to lung cancer, 2,487 to breast cancer, 1,895 to prostate cancer, and 3,276 to cancers of the colorectal system; these four types of cancer accounted for 53.2 percent of all cancer deaths. The top cancer killer of both men and women was cancers of the lung, trachea, and bronchus, while the second most-fatal was prostate cancer for males and breast cancer for females.[1] It is estimated that 1,220,100 new cases of cancer will be diagnosed in the United States in 2000, with 74,359 of these new cases in Texas.[2] Of the U.S. population, it is estimated that half of all men and one-third of all women will develop cancer in their lifetimes, and millions of people are living with cancer or are considered cured.[3] Some of these cancers are completely preventable, and the financial, physical, and emotional impact of many others could be lessened if more people practiced prevention and early detection measures.

"Primary prevention" refers to efforts to prevent cancer from developing, such as avoiding known risk factors, like smoking, and taking measures to lower one's risk, such as regular exercise and healthy eating habits. "Secondary prevention," also called early detection or screening, includes testing to locate the presence of cancerous cells as early as possible, while they are still localized and can be treated most effectively. There has been much research, discussion, and debate among health professionals regarding cancer prevention. Issues with primary prevention include identifying cancer-causing agents and determining how much exposure causes health risk in humans, and how to persuade people to avoid risky activities if they are associated with pleasure and would require behavioral changes, such as quitting smoking or limiting exposure to the ultra-violet rays in sunlight. Issues with secondary prevention include how much invasive medical testing should be done on asymptomatic individuals, which individuals should be targeted for screening and what are the optimal intervals, which tests are most effective, and which costs can be justified when most people screened will test negative for cancer and some tests may have harmful side effects.

The following sections discuss cancer prevention and early detection guidelines, strategies, and issues, including details on lung cancer, breast cancer, prostate cancer, colorectal cancer, and others as appropriate. Information is also included on analyzing the cost-effectiveness of prevention efforts, and the last section discusses issues in calculating the economic impact of primary and secondary prevention.

Primary Prevention

Guidelines and Strategies

As "cancer" actually consists of more than 100 different diseases in all parts of the body, there is no concise way to describe prevention and early detection methods for all of them, and a wealth of information is already freely available on these topics. Although genetics is a factor in the development of many cancers, heredity alone does not explain cancer; behavioral factors modify the risk of cancer at every stage. Evidence shows that about one-third of the approximately 500,000 annual cancer deaths in the U.S. is due to cigarette smoking and another third is due mainly to dietary factors; the remaining third is influenced by many factors including sun exposure, hormones, infections, and occupational hazards.[4] Since a majority of the population does not smoke, nutrition and physical activity are the most important overall behavioral determinants of cancer risk in the general population.[5]

Only 10 to 20 percent of all cancers are caused by inherited mutations (present in almost all cells in the body from birth) and naturally-occurring somatic mutations (mistakes in cell division occurring after birth, so present only in the cells descending from the mutated cell). The other 80 to 90 percent of cancer cases are caused by somatic mutations of cancer-related genes that happen due to environmental exposure to cancer-causing agents, or carcinogens. It has been determined that five or more genes must be mutated before malignant transformation starts in most adult cancers, but as few as two mutated genes may cause some childhood cancers.[6] As carcinogenesis, the process of developing cancer, becomes more understood, it is hoped that genetic therapies will be developed that can interfere in key steps of this process or undo damage to cells. Until this happens, the only known activities that might aid in the prevention of cancer are decreasing exposure to carcinogens (avoiding them and imposing restrictions on their production), increasing exposure to beneficial chemicals, and detecting and treating precancerous conditions early.

Cancer risk is affected by many dietary factors, such as types of food eaten, how the food was prepared, portion size, and overall caloric balance. Limiting meat, dairy, and other high-fat foods; and eating more plant-based foods such as fruits, vegetables, beans, and grains; and balancing calories and physical exercise can reduce cancer risk, but many Americans do not follow these principles. The American Cancer Society Advisory Committee on Diet, Physical Activity, and Cancer put forth guidelines in 1998 for people age 2 and over to reduce cancer risk (see Table 1). Though no diet can guarantee complete defense again a disease, these guidelines are based on scientific studies and are consistent with other health agencies' recommendations on healthful practices and the prevention of other diet-influenced conditions such as heart disease and diabetes.[7] The National Cancer Institute, Department of Agriculture, and other organizations also have similar dietary guidelines.

Table 1. American Cancer Society Guidelines on Diet, Nutrition, and Cancer Prevention

1. Choose most of the foods you eat from plant sources.
   - Eat five or more servings of fruits and vegetables each day.
   - Eat other foods from plant sources, such as breads, cereals, grain products, rice, pasta, or beans several times each day.
2. Limit your intake of high-fat foods, particularly from animal sources.
   - Choose foods low in fat.
   - Limit consumption of meats, especially high-fat meats.
3. Be physically active: achieve and maintain a healthy weight.
   - Be at least moderately active for 30 minutes or more on most days of the week.
   - Stay within your healthy weight range.
4. Limit consumption of alcoholic beverages, if you drink at all.

Source: ACS, "The Importance of Nutrition In Cancer Prevention," http://www2.cancer.org/prevention/NutritionandPrevention.cfm.

Many studies have shown an association between lack of adequate consumption of fruits and vegetables and increased risk of many cancers as well as other conditions like cardiovascular disease. The quarter of the population with the lowest intake of fruits and vegetables was shown to have about twice the rate for most common types of cancer than the quarter with the highest intake. The benefits are thought to be due to antioxidants and other beneficial micronutrients that can help to repair DNA damage.[8] Conversely, a high-fat and high-calorie diet and the resulting effects on obesity and hormone production has been linked to several cancers, including those of the breast, prostate, ovary, and endometrium. Though dietary factors are important in many cancers, few of these have been unequivocally linked to specific human cancers. Therefore, while the above guidelines and others can be recommended for overall good health and cancer prevention, it is not possible to recommend certain foods or physical activities to specifically prevent breast cancer, prostate cancer, or most others. However, specific primary prevention measures can be effective in at least several cancers, including skin, colorectal, and lung cancers.

The main prevention for melanoma and other skin cancers is limiting exposure to ultraviolet (UV) light in sunlight and tanning booths, especially for people with light skin (people with dark pigment have a low incidence of skin cancer). Protective clothing and avoiding sun exposure in the middle of the day is recommended, and though the exact effect of sunscreen is not known, it does prevent serious sunburns associated with melanoma. Therefore, it is recommended that people use a water-resistant sunscreen with a sun-protection factor (SPF) of at least 30 when outdoors.

Several studies have shown that NSAIDs (nonsteroidal anti-inflammatory drugs, like aspirin and ibuprofen) may prevent colorectal cancer.[9] Not enough evidence currently exists for aspirin to be recommended to everyone for this purpose, but people at high risk or others who are interested might want to consider taking one aspirin per day (which may also help prevent heart attacks and strokes). Though evidence for a protective effect of dietary fiber against colon cancer has been shown in comparative studies and animal studies,[10] this is not completely conclusive or understood, as several

recent studies have shown no significant effect, and that a certain type of fiber (found in some supplements but not in the average diet) may even increase the incidence of malignant colon tumors in people with adenomas (precancerous growths).[11] Extra calcium may also help prevent colorectal cancer, but this is still under investigation.

Tobacco smoke is a major cause of cancer deaths, as stated above. It is estimated that smoking accounts for 80 to 90 percent of lung cancers, so smoking cessation and tobacco control are obvious and effective prevention measures for lung cancer. Lung cancer is unique in that it has an obvious etiology and clear risk reduction actions for a majority of the cases, yet economic, political, and social factors make control difficult.[12] In the early 1900s, before the introduction and widespread availability of manufactured cigarettes, lung cancer was rare. Smoking is also associated with cancers of the oropharynx, esophagus, pancreas, kidney, bladder, and cervix. It is estimated that 91 percent of adult smokers had their first cigarette before age 20, and smoking among youth is increasing even as it decreases among the general population.[13] About 3 million (22 percent) adults in Texas over age 18 smoked cigarettes in 1998, and this number increases when other forms of smoking and those under 18 are taken into account.[14]

More than 3500 chemicals and more than 55 potential carcinogens have been identified in tobacco smoke.[15] The longer a person has smoked and the more packs a day smoked, the greater the risk of getting lung cancer. The lungs of people who quit smoking gradually start returning to normal, though after 10 years they are still at higher risk for lung cancer than a person who never smoked, and their risk for lung cancer as well as heart disease remains higher for as long as 25 years.[16] Exposure to second-hand smoke also increases the risk of lung cancer; a spouse of a smoker has a 30 percent higher risk of developing lung cancer than a spouse of a nonsmoker. Marijuana cigarettes have more tar than regular cigarettes and thus are also a risk, though it is difficult to obtain clear data because they are illegal and unregulated, and also many people who smoke them also smoke tobacco, making it hard to differentiate the effects.[17] One effect of smoking that many people do not know or do not consider is that men who smoke (as well as those with inadequate diets such as a vitamin C deficiency, which is sometimes linked to smoking) may cause damage to not only their somatic DNA but the DNA in their sperm. Therefore, smoking by fathers-to-be may increase the risk of birth defects and childhood cancers in their children.[18]

Personal and family history of lung cancer is a risk factor, though in families with smokers it is difficult to tell if the increased risk is due to heredity or exposure to smoke. The lung cells of women may have more of a genetic predisposition to develop cancer when exposed to tobacco smoke than men, several studies have shown, thus women may be more likely to develop lung cancer than men under the same circumstances. People acquire mutations all the time, from environmental factors and as cells reproduce and damage to DNA occurs, however, most of these are corrected by repair enzymes and many are harmless. But if cells are exposed to too many carcinogens, such as from tobacco smoke, they may be weakened or be growing too fast, and all mutations may not be fixed. Cancerous tumors can form in the lungs (as well as other areas of the body), and other mutations may make some cancers likely to spread faster and become more invasive.[19]

Another risk factor for lung cancer is exposure to asbestos fibers, which can cause a cancer of the pleura called mesothelioma. Asbestos workers are seven times more likely to die of lung cancer than the general population, and asbestos workers who smoke have a greatly increased risk of getting lung cancer—50 to 90 times greater than the general population.[20] Radon, a naturally-occurring gas formed from radium during the decay of uranium, can increase risk for lung cancer. Radon outdoors is not a problem, but it can become concentrated indoors when it diffused through the ground up into basements and walls and becomes trapped in homes in some regions. Increased risk also results from other gases and chemicals that miners and other workers may be exposed to such as uranium, arsenic, vinyl chloride, mustard gas, talc, and coal products.

The inflammation and scarring caused by tuberculosis and some types of pneumonia can cause increased risk of adenocarcinoma. Air pollution was estimated to cause 1 to 2 percent of all lung cancers, and this will decrease as more attention is paid to the environment, thus pollution is not felt to be an important factor in lung cancer.[21] Most other chemicals found in water pollution and foods are also not a significant cause of cancer. It is estimated that more than 99 percent of the chemicals that people ingest, including pesticides, are natural and not synthetic in origin, and that at least half of all chemicals that have been tested, whether natural or man-made, and even those that occur in fruits and vegetables, can be shown to be carcinogenic in rodents if given in high enough doses. There is growing evidence that this carcinogenicity is due to the high dose itself (much higher than a human would ever ingest) causing tissue injuries and more rapid cell division, and later cancer, and not the chemical itself.[22]

Quitting smoking is the most obvious prevention strategy for most lung cancers, and another important strategy is for people who work around substances that may cause cancer to take appropriate protective measures. People living near natural uranium deposits should get their homes tested for radon gas. Even if all of these risk factors are minimized, there will still be some people who develop lung cancer for no apparent reason. These cases could perhaps be minimized if more people followed the general guidelines for good health and diet and lowering one's cancer risk from the American Cancer Society and others, as stated above. A newer area of research is chemoprevention, the use of natural or synthetic chemicals to prevent, inhibit, or reverse cancer. The National Cancer Institute is currently studying over 450 compounds in the laboratory, and about 40 in clinical trials. The four categories of preventive agents with the highest priority for research are nonsteroidal anti-inflammatory drugs (NSAIDs like aspirin, as mentioned above in connection with colorectal cancer), calcium compounds, retinoids (which are related to vitamin A), and hormonal agents such as selective estrogen receptor modulators (SERMS, such as tamoxifen and raloxifene).[23] These drugs show promise in fighting some cancers, but the effects are complicated and may not be clear-cut. For example, tamoxifen was shown to decrease the risk of breast cancer in high-risk women, but it increased the risk of endometrial cancer, and vitamin A and beta carotene were tested as preventive agents for lung cancer but both were found to actually increase the risk of lung cancer among smokers. Much more research is needed in the area of chemoprevention, and the current clinical trials and their results will take many years to complete and analyze.

Important Issues with Primary Prevention

Primary prevention sounds simple in theory but is actually a very complex area to study. When real people are involved there are many variables to control that could be helping to cause or inhibit the effect, in this case the development of cancer. There are many biological processes and relationships that are not fully understood, since people that are apparently very healthy can develop cancer, and others with unhealthy habits may never get cancer. Results that hold true in chemical tests or in laboratory animals may not be the same in humans, and even if they are, they could take many years to appear, as cancer becomes more likely as a person ages. Clinical trials (meaning human subjects) are difficult to manage because thousands of subjects must be recruited and enrolled into studies to demonstrate risk reduction, and they must be monitored for many years. Even in non-clinical prevention efforts like education programs, results will not be seen overnight. It is estimated that it takes 20 to 30 years to see a decline in lung cancer rates after smoking declines in a population.[24] Prevention is best thought of in the context of long-term goals, and there are no guarantees with current prevention methods, only the promise to "reduce" risk.

Cost-Effectiveness of Primary Prevention

Cost-effectiveness of primary prevention is difficult to calculate due to the reasons stated above. Since the timeframe is very long term (preventing cancer over a person's entire lifetime), many other variables come into play, both known and unknown, and these could also effect other conditions like heart disease, making it difficult to quantify and separate the effects of prevention measures. Since the intervention often occurs early while the health benefits usually happen later in life, it is necessary to apply a discount rate to the future benefits and costs so that all amounts are expressed in the present value. Because of this discounting, prevention with shorter-term benefits and savings will often have more favorable cost-effectiveness ratios than preventive measures with longer-term benefits and savings.[25] By the same token, prevention often gets short shrift compared to treatment because treatment is for identifiable individuals in the present while prevention is for statistical individuals with benefits to be realized in the future.

Many primary prevention initiatives such as physical education in schools, dietary advice, and promotion of protected sex are not likely to be found particularly cost effective in themselves if the only benefits one is measuring are the reduction of morbidity and mortality due to cancer. They have an impact over many years, whole populations receive them, and only a small number of cancer sufferers will be affected. This is not to say that these are not worthwhile initiatives. Other benefits such as reduction in heart disease, stroke, diabetes, and other conditions may also occur due to these initiatives and should also be figured into the calculus.

To calculate the cost effectiveness of a particular initiative, say the health gains of banning junk food from public schools, one would have to make the following calculations using what has become standard cost-effectiveness methodology:[26]

(1) The net cost of the action proposed; this should include the discounted present value of the incremental cost of this action now and in the future. In this example it might require the cost of hiring additional school cafeteria personnel and foregoing contributions to the school by snack food and beverage companies. This might require raising taxes or spending less on other programs. If we are looking at the intervention from the point of view of society, then savings to children and families of not buying junk food at school should be factored in.

(2) The costs to be measured should be related to the population being studied. For instance, if we are looking at the school population who would be in first grade in 2001, then we would apportion the net present value of cafeteria costs to the school for that population for the next 12 years. From these costs we can subtract the present value of the net change in treatment costs over a lifetime that would be averted due to improved nutrition during school years.

(3) The effectiveness part of the equation estimates the change in discounted quality-adjusted life years from the initiative. Since the health benefits will be realized far into the future and discounted to the present, the calculations will be difficult. The improved nutrition depends on the quality of food that these children consume after the change, and many children will continue to eat unhealthy food elsewhere. The exact link between childhood nutrition and specific health outcomes is difficult to establish. Similarly, the course of these outcomes is difficult to date, cost, and predict. In any case, in this and similar analyses the indirect cost of cancer or other diseases are not included in the denominator of quality-adjusted life years. In other words, lost current and future earnings due to disease are not part of the cost-effectiveness analysis.

It is unlikely that many primary prevention strategies will "pay for themselves." In order to do this the savings in treatment costs would have to exceed the primary prevention expenditures. But even if they do not completely pay for themselves, they may be a much better value than the treatment costs because they may also be associated with a much higher quality of life and yield a higher return for the dollar. One strategy that seems to be a very good value is implementing smoking prevention and cessation programs, especially for young people and for persons who currently smoke. A study commissioned by the Texas Division of the American Cancer Society estimated that a four-year tobacco prevention program costing $200 million from Texas' tobacco settlement money recommended by the Texas Inter-Agency Tobacco Task Force was likely to save $440.5 to $972.7 million in long-term costs to the Texas Medicaid program.[27] These amounts were for adults only and did not take into account secondary benefits such as fewer low-birth weight babies and effects from second-hand smoke, so savings are likely to be even higher. Another study found that smoking cessation counseling costs $5,429 to $15,833 per year of life saved, a relatively cheap cost compared to many other interventions.[28]

In looking at and proposing primary prevention strategies it is important to look at the world over time with these strategies and without them. Although it might seem difficult to deny problematic tertiary treatment now for medical conditions in order to fund prevention strategies it will be far crueler to limit treatment more drastically in the future if those conditions become far more prevalent due to inadequate prevention initiatives.

Secondary Prevention/Early Detection

Guidelines and Strategies

Many different screening tests exist for the early detection of cancer in individuals who have a higher risk of a certain cancer or in whom cancer is suspected due to their symptoms. These are specific to different types of cancer and are administered on an individual as-needed basis, so they will not be discussed here except where they overlap with the screening recommended for the general population (for example, the same procedure, a mammogram, is called a diagnostic mammogram if given to a women in whom breast cancer is suspected, and a screening mammogram if given to an asymptomatic woman). The American Cancer Society has developed general guidelines for screening asymptomatic people for several of the most common cancers. Guidelines for four cancers are listed below; most other cancers do not have reliable and specific early detection methods, other than visual and manual detection for skin cancers or others on or near the surface of the body. Many cancers, such as lung, brain, ovarian, and pancreatic cancer, are usually detected only when the cancer is far enough along for the symptoms to become noticeable, which is usually in the advanced stages.

Table 2. ACS Guidelines for Cancer-Related Check-Ups for Asymptomatic Individuals

Test or Procedure	*Age*	*Frequency*
Breast Cancer (female)		
Breast self-exam	20 and over	every month
Clinical breast exam	20-39; 40 and over	every 3 years; every year
Mammography	40 and over	every year
Cervix Uteri (female)		
Pap test	sexually active or 18 and over	every year *(may be less frequent after 3 or more normal results)*
Pelvic exam	sexually active or 18 and over	every year
Colon and Rectum (male and female)		
One of the following five options: *(option 3 preferred by ACS; a DRE should be done with options 2-5)*	*(People at high risk may need to begin testing earlier)*	*(People at high risk may need to be screened more frequently)*
1. Fecal occult blood test (FOBT)	50 and over	every year
2. Flexible sigmoidoscopy	50 and over	every 5 years
3. FOBT every year plus flexible sigmoidoscopy	50 and over	every 5 years
4. Double contrast barium enema	50 and over	every 5 years
5. Colonoscopy	50 and over	every 10 years
Prostate (male)		
Digital rectal exam (DRE) and prostate specific antigen blood test (PSA)	50 and over *(men with high risk should begin testing at age 45)*	every year *(if life expectancy is at least 10 years; given with information about benefits and risks of testing and treatment so men can make informed decisions*)

Adapted from: American Cancer Society, *Cancer Facts & Figures 2001*, p. 35.

The five-year survival rate for these four cancers and the other three for which the American Cancer Society has early detection recommendations (testes, skin, and oral cavity) is 81 percent (excluding people who die of other causes). Cancer prognosis is greatly improved by early detection, and they estimate that if all Americans followed these recommended screening guidelines that the five-year survival rate for these cancers would increase to about 95 percent.[29] Some other organizations' recommendations differ somewhat from those of the American Cancer Society, as stated in the following sections on specific cancers and their screening methods.

Breast cancer is the most common cancer in women, though lung cancer has replaced it as the most deadly. Since 75 percent of breast cancer cases occur in women with no high-risk factors, all women should be screened for breast cancer. Mammography will not identify 10 to 15 percent of breast cancers even in the best circumstances, so this screening method should be combined with clinical exams and self-examination for the best outcome.[30] Screening is effective in breast cancer because it has recognizable preinvasive stages that are highly curable: ductal carcinoma in situ and lobular carcinoma in situ. Even patients with early stages of invasive cancers often survive for a long time after diagnosis, but women diagnosed with stage III or IV cancer usually have a poor prognosis. Even though mammograms are relatively expensive for a screening test and are not perfect (no tests are), they have been shown to be effective in reducing breast cancer mortality, and there is no argument among cancer organizations in recommending that women over 50 have them every 1 to 2 years.

There is some controversy, however, on how effective mammography is for women under age 50. Some studies show little or no effectiveness of mammograms in ages 40-49,[31] while others claim there is some benefit but it may not be cost-effective.[32] Although the American Cancer Society recommends annual mammograms after age 40, some other organizations recommend starting at age 50, including the American Academy of Family Physicians. The National Cancer Institute looked at a number of clinical trials spanning three decades and enrolling 500,000 women ages 40 to 69, and meta-analysis showed the following results: mammograms in women aged 50-69 reduced mortality by 30-35 percent, and in the 40-49 age group mortality was reduced by 17 percent overall, though some studies saw no difference (there is not enough evidence for recommendations over age 70). Recommendations from a National Institutes of Health Consensus Development Conference on Breast Cancer Screening in 1997 contained a majority report stating that there was not enough evidence to recommend universal screening of all women in their forties, and a minority report that believed the data did support screening in this age group (both sides agreed that if women in their forties wanted mammograms, their insurance should pay for them). The National Cancer Institute compromised by saying that women "in their forties or older" should get regular mammograms every one to two years, and should start earlier if they have increased risk and it is recommended by their doctors.[33]

A very new method developed by Dr. Susan Love for detecting the earliest stages of breast cancer and precancer (years before it is likely to show up on mammograms) is called ductal lavage. It involves inserting a very thin catheter into the milk ducts of the breast where cancer originates, washing them out

with a saline solution, and then examining the cells that are washed out for abnormalities. It is reported to take about 15 minutes and be less painful than a mammogram, and it is hoped that eventually drugs could be introduced directly into the ducts to kill abnormal cells before they become malignant.[34]

Lung cancer is not the most commonly diagnosed cancer in Texas, but it is the most fatal, often due to it being detected later than other cancers, and thus at less treatable stages.[35] Developing effective early screening programs for lung cancer could save many lives, as recognizable symptoms usually do not appear until the disease has spread to other parts of the body. Currently, only about 15 percent of lung cancers are found in the early stages before it has metastasized, and many of these are found incidentally, during testing being performed for other medical conditions such as heart disease or pneumonia. If lung cancer is found and treated before it has spread to the lymph nodes, the five-year survival rate is 50 percent, but since most cancers are not found this early, the overall five-year survival rate for all lung cancers is only 14 percent.[36]

Chest x-rays and sputum cytology can be used to screen for lung cancer, but eight studies over the last 40 years have shown that these do not usually find lung cancers early enough to improve the patient's prognosis, so screening is not a routine practice even for those at higher risk.[37] There continues to be debate surrounding this issue, however, especially for those at high risk such as heavy smokers.[38] While this continues to be debated, there seems to be more agreement (in the U.S. at least) that current lung cancer screening methods should not be implemented in the general population at this time. About 30,000 subjects were enrolled in several of these early studies in the 1970s and 1980s, and even though the initial results were not promising, sputum samples were saved and reexamined later to compare cells from patients who later developed cancer to those who did not. These new studies have shown some biomarkers that are helpful in predicting later development of lung cancer, and research continues on these and other new methods for identifying early lung cancer cases.[39]

Prostate cancer is the most common cancer in men in the U.S., though it is not the most deadly. The incidence of prostate cancer is rising annually due to more early detection occurring, but there are controversies surrounding early detection and follow-up treatments. These stem from the fact that many, and possibly most, men over age 50 have some histologic evidence of this cancer, but clinically significant prostate cancer is much less prevalent.[40] Therefore, clinically insignificant prostate cancer is often detected and can lead to unnecessary treatment. Patients with advanced prostate cancer have a poor prognosis, but it is not clear that aggressive management of small non-aggressive cancers affects survival, though it does impair quality of life. Only one-tenth of the men believed to have prostate cancer actually die from it (thus the reason it is said that more men die with prostate cancer than from it).[41]

As far as screening methods for prostate cancer, digital rectal examination (DRE) is quick, safe, and inexpensive when done with an annual physical exam, but it has a rather low sensitivity and specificity, so it is recommended that it be combined with the prostate-specific antigen test (PSA). This test has a high positive predictive value, but the problem remains that there is not enough information currently to

distinguish between indolent cancers that would be best managed by observation or "watchful waiting" and more aggressive cancers that need early intervention. The PSA test has not demonstrated that it results in reduced mortality, but it is still used by many physicians as an integral part of preventive care for men.[42] Though the American Cancer Society recommends screening for all men over age 50 (with the new caveat that they must agree to it and make an informed decision by being given information on benefits and risks of testing and treatment), the National Cancer Institute, the U.S. Preventive Services Task Force, and the American Academy of Family Physicians all believe that no general recommendation for screening should be made, and that the choice of whether average-risk men should get regular PSA tests should be left up to the individual men and their doctors.[43]

Over 90 percent of *colorectal cancers* start out as benign adenomatous polyps that progress to carcinoma. The adenoma stage is highly curable with surgery to remove the polyps, but once carcinomas infiltrate and metastasize, prognosis is poor. If screening is regularly performed and adenomas are identified in time and removed, and if these people keep receiving colonoscopies or other screening periodically, in theory almost all cases of colorectal cancers could be prevented.[44] The fecal occult blood test is not a very conclusive or accurate cancer screen in itself, because many non-cancerous conditions such as diverticulitis and peptic ulcers can also cause blood to appear in the feces, and adenomas and carcinomas may not always bleed, but it is simple and non-invasive and is useful in detecting large lesions and to select people for further testing. Flexible sigmoidoscopy permits direct visualization of the closer part of the colon and can detect about half of all colorectal cancers (virtually all of those in the first 60 centimeters of the colon). Studies have shown that periodic sigmoidoscopic screening can reduce overall colorectal cancer mortality by about one-third (a 70 to 80 percent reduction in the half that are detected). Colonoscopy is a more expensive and invasive procedure, but it allows all of the colon to be examined in most patients. However, the risk for perforation of the colon is 1 in 1,000 procedures, and about 1 to 3 of 10,000 patients receiving colonoscopies die of complications.[45] Some people have suggested that it only be done once, between ages 50-60, and others contend that a high-quality, double-contrast barium enema exam is a safer, less time-consuming, and less expensive alternative. Small lesions are difficult to identify with the barium enema, however, and not all radiologists are skilled in this area.[46]

A very recent breakthrough just tested at the Mayo Clinic may eventually replace the more expensive and invasive procedures for detecting colon cancers. The new method, which involves DNA testing of discarded cells in stool samples, was reported to have very high accuracy rates and no false positives in an initial trial; a large-scale clinical trial of this method, sponsored by the National Cancer Institute, will begin in January 2001.[47] Up to 5 percent of colorectal cancers are caused by hereditary colorectal cancer syndromes, and it is especially important for these people to receive regular screenings; however, only about half of the general population who is eligible for screening actually gets screened, so more education is needed of both physicians and consumers. New methods that are cheaper and noninvasive, like this DNA detection and a new method undergoing testing called a virtual colonoscopy (combining imaging like a CT scan with a virtual reality computer program to give realistic 3-D images of the colon),[48] are expected to increase screening compliance.

There are some *other cancers* where early detection has been shown to be efficacious. Cervical cancer deaths have decreased dramatically since the Pap (Papanicolaou) test was developed in the 1930s and became routine in the 1960s; it is estimated that 70 percent of cervical cancer deaths have been prevented in the United States (this cancer is still a major killer in developing countries). This test detects precancerous changes in cells (called CIN, or cervical intraepithelial neoplasia) and allows for early localized treatment of the areas before they become invasive. Skin cancer incidence has risen dramatically since the 1950s, and most of the skin cancer deaths in the U.S. are due to melanoma. Visual screening and palpation methods are quick, painless, and inexpensive, and most small cutaneous melanomas as well as premelanomas can be cured by surgical removal. The benefits and costs are still being investigated, and examinations are recommended every three years from ages 20 to 40 and every year after age 40, along with self-examination and a reporting of any suspicious changes in the skin. More research is needed on effective screening strategies for many other cancers, and thus screening of asymptomatic people is not currently recommended; these include ovarian, endometrial, pancreatic, stomach, liver, and esophageal cancers.

Important Issues with Screening

The goal of screening is the early detection and treatment of a cancer, with a corresponding reduction in the mortality rate. There are two requirements for an effective cancer screening program: one is that the screening test must detect cancer in an early stage, and the other is that the treatment resulting from this detection must be more effective than treatment given at a later time when cancer is usually diagnosed.[49] Screening for some cancers meet both of these criteria (for example, breast and cervical), but others meet only one or neither (for example, lung and prostate). There are both advantages and disadvantages to cancer screening, even if effective. Advantages include an improved outcome for some patients, including those who would have died without the early detection of their disease; less radical treatment, and thus fewer resources and costs that might be used in some cases of cancer; and reassurance for those with negative test results. Disadvantages include a longer period of morbidity for patients whose outcome does not change, overtreatment of borderline abnormalities (causing higher direct and indirect costs), false reassurance for those with false-negative results (who may tend to dismiss subsequent symptoms, delaying treatment), unnecessary morbidity for those with false-positive results, and side effects of the tests themselves.[50] All of these factors must be evaluated before instituting screening policies.

Screening programs for the general population should be considered only if the following conditions are met: the disease in question is a serious problem in the population; an effective treatment is available; the screening procedure is safe, rapid, inexpensive, and relatively easy; the test can be monitored and reproduced; and the test performance is acceptable. Performance can be measured by three standards: sensitivity, specificity, and positive predictive value. *Sensitivity* is the proportion of people with the disease who test positive, *specificity* is the proportion of people who do not have the disease who test negative, and the *predictive value of a positive test* (PVP) is the proportion of those testing positive who

actually have the disease, which is a function of sensitivity (Se), specificity (Sp), and disease prevalence (P). The mathematical relationship between these measures is PVP = PSe/[PSe + (1-P)(1-Sp)].[51] For screening, high specificity is more important than high sensitivity, while in using the same test for monitoring after treatment, high sensitivity is more important than high specificity. However high or low they may be, the screening test properties should be tested and known in advance.

Even if screening properties are very high, this does not indicate anything about what effect the screening will have on the consequences of the particular cancer in question. For example, a nonprogressive preclinical disease state (as is often seen in prostate cancer) is more likely to be detected by routine screening but is not likely to cause death, so identification and treatment may be more harmful than not getting treatment. Once a screening test is implemented, it can be included into a program of treatment and follow-up, which must then be evaluated in terms of its effect on cancer mortality.[52] There are several types of biases that can complicate evaluation of screening programs: *Lead-time bias* refers to the amount of time that screening advances the diagnosis of the disease, so that it may appear that people who were diagnosed through screening lived longer than those diagnosed later, even if they would have died at the same time. *Length-biased sampling* refers to the fact that a single screening is more likely to detect slow-growing, non-aggressive cancers because of their higher prevalence in the population, so these people will also appear to live longer, though this may be due more to their type of cancer than the fact that it was detected early (this bias can be minimized through repeated screenings over time). *Overdiagnosis bias* refers to an increase in length-biased sampling so that the screening test threshold is lowered and non-aggressive tumors that may never cause a problem are identified.[53]

There are still many obstacles to screening becoming a major contributor to cancer control, including the unfavorable natural progression of many cancers, poor compliance of those most at risk, economic barriers, and problems with the tests themselves (such as costs and morbidity resulting from false positives, false negatives, and side effects). Three of the screenings most likely to make an impact on cancer mortality are those for breast, cervical, and colorectal cancers, but there are many more that are inconclusive. Since screening has the potential to offer a more rapid return than primary prevention, however (since this may take decades more to be fully understood), secondary prevention and continued research on it should remain a priority.[54]

Cost-Effectiveness of Screening

There are several different ways to do comparative health economic analyses. One of these, cost-effectiveness analysis, is the ratio of health benefit to cost of the intervention, with benefit measured in terms of clinical outcomes (such as illness prevented or deaths averted), not cost.[55] This approach generally assumes that society has limited resources and that other programs are under consideration, and they are ideally analyzed after a randomized trial has demonstrated a reduction in mortality from a screening method. Calculating cost-effectiveness for cancer screening is complicated, and cost-

effectiveness should not be the only deciding factor for funding; ethical and political issues must also be considered.

Cost-effectiveness analysis attempts to estimate the net cost of the policy or intervention per additional quality-adjusted life year added. (When quality-of-life information is not available, cost-effectiveness is sometimes calculated and reported in "life years saved" instead of "quality-adjusted life years saved.") This analysis is basically a ratio of the difference in costs to the difference in effectiveness between two interventions, or an intervention and no intervention. The equation that summarizes the calculations is the following:[56]

$$C/E = \frac{\Delta C + \Delta C_{SE} - \Delta C_{morb} + \Delta C_{LE}}{\Delta Y - \Delta Y_{SE} + \Delta Y_{morb}}$$

The variables in this equation are defined as follows:

C/E = The cost per quality-adjusted life year of the proposed intervention as compared to the status quo.

ΔC = The present value of the cost of the proposed intervention.

ΔC_{SE} = The present value of the cost of treating side effects of the intervention.

ΔC_{morb} = The present value of the costs saved from not treating conditions that were prevented or ameliorated.

ΔC_{LE} = The present value of the additional costs to the medical care system of caring for conditions that would not have occurred if the person had not lived longer.

ΔY = The present value of the change in life years due to the intervention.

ΔY_{SE} = The adjustment for changes in quality of life due to the side effects of treatment.

ΔY_{morb} = The adjustment for changes in quality of life due to the reduction or prevention of disease.

The value of conducting cost-effectiveness analysis systematically is that it permits the analyst to compare a number of different initiatives. Generally the analysis should be done from the perspective of society as a whole. The following table summarizes the different components of cost-effectiveness analyses and offers a definition of each and other comments.

Table 3. Factors in Cost-Effectiveness Analyses

Variable	Definition	Measurement	Issues
Reference case or status quo.	The base from which the net costs and benefits of a change in services or policy are measured.	May be current treatment protocol or payment policy.	Not always easy to characterize.
Proposed initiative or policy and the population affected	Clearly specify the nature of the proposal and which persons will be affected or eligible over time. Need to define clearly.	Need to specify the deviation from the status quo or reference case.	Must also include others who may be affected indirectly (e.g., elderly may be negatively affected by nutritional additives to cereals to benefit youths).

Variable	Definition	Measurement	Issues
Cost of the initiative or policy	The net cost of the change being analyzed.	Add all the additional costs relative to the status quo. Include all incremental costs of screening, prevention, and treatment, and net costs of caring for the illness discounted to the present.	Whether to include cost of caring for other conditions in persons who live longer than they could have expected due to the intervention. Need to estimate future costs that may depend on compliance. May not be able to accurately measure future costs because of 1) cost saving breakthroughs or 2) cost enhancing extended morbidity.
Effectiveness of the initiative or policy	Increase or decrease in quality adjusted life years.	Present value of expected change in quality adjusted life years. Need method of estimating quality adjusted.	Difficult to know relative impact of the initiative, need to make assumptions about compliance, efficacy of alternatives, and risks to life from other causes if life is extended.
Discounting percentages	The rate at which future costs and quality adjusted life years should be discounted to the present.	Usually value future costs in today's dollars so only discounting at 2-3% for the time value of money.	Need to discount future quality adjusted life years since they are evaluated relative to discounted dollars.
Sensitivity analysis	The extent to which the results of the analysis depend on the assumptions.	Vary different parameters and see what different results are generated.	Need to see if results are dependent on cost estimates, compliance estimates, efficacy estimates, and discounting values.

The cost-effectiveness estimates given below for various cancers use different methods, discounting rates, and dollar-years, and are provided for rough comparison only. The decision about what the boundary is between a cost-effective intervention and one that is not cost-effective is mainly political, reflecting the value of health to the particular society, as well as its affluence. This threshold is not usually explicitly stated, but it can be somewhat divined by analyzing the health coverage decisions of governmental and private payers. In the U.S., well-established procedures like mammograms and dialysis generally have cost-effectiveness ratios of $50,000 or less per LY saved, while those costing more than $100,000/LY are usually considered cost-ineffective (too expensive for the amount of benefit gained) and are not covered by insurance. The cost-effectiveness of procedures with ratios between $50,000 and $100,000 is not as clear-cut and can depend on the situation, and coverage varies.[57] As tertiary and chronic interventions become more expensive, the calculus of cost-effectiveness will seem to show that prevention is now more cost-effective. It must be remembered that this is ironically an artifact of the decision to pay for the most expensive interventions.

There are a variety of estimates for cost-effectiveness of secondary prevention. One study shows the cost-effectiveness of colorectal screening to be about $40,000 per life-year saved,[58] while another estimated $28,848-113,348 per LY saved (the screening methods were not given).[59] In people aged 65, a study showed an annual fecal occult blood test (FOBT) to cost about $35,000 per life-year gained.[60] Another study calculated the cost-effectiveness of a variety of screening techniques for colorectal cancer

in white men with 60 percent compliance. They found that FOBT plus a sigmoidoscopy every five years (with follow-up colonoscopy if any suspicious polyps were seen) costs about $51,200 per LY gained, while the same screening every 10 years costs $21,200 per LY. The sigmoidoscopy alone every 10 years (with follow-up colonoscopy for all polyps) costs about $16,100 per LY saved.[61]

Annual mammography was found by one study to cost about $34,500 per life-year saved.[62] Another study estimated that screening mammography costs about $20,000 to $50,000 per life-year saved,[63] while another found that a combination of annual mammograms and clinical breast exams (followed by treatment as needed) prevents premature death at a cost of $22,000-$84,000 per life-year gained in women age 55-65.[64] Cervical cancer screening (presumably pap smears) were found by one study to cost $33,572 per life year saved.[65] Another study showed a cost of $40,000 per LY gained for annual cervical cancer screening, and a cost of $14,000 per LY for screening every three years (age 20-75) for average risk women. Screening every three years is almost as effective as screening annually (reduction of invasive cervical cancer by 91.2 percent vs. 93.3 percent).[66]

A study on prostate cancer calculated cost-effectiveness ratios for prostate cancer screening that vary by age and cure rate of prostate cancer. For men aged 50-59, the cost per quality-adjusted life-year gained was $16,029 (assuming 100 percent cure rate) and $24,868 (assuming 75 percent cure rate). For ages 60-69, the cost per quality-adjusted life-year gained was $27,507 and $46,976 for 100 percent and 75 percent cure rates, respectively. For ages 70-79, the cost per QALY was found to be $162,095 (100 percent cured) and $612,095 (75 percent cured).[67] Another study calculated cost per life-year saved by prostate screening (PSA and DRE) and treatment. Its cost ranges per LY (not quality-adjusted) are again given per age group: $2,339-$3,005 for ages 50-59 and $3,905-$5,070 for ages 60-69.[68] The figures are much higher in the quality-adjusted costs because men often live for a long time after prostate cancer detection and treatment (whether or not cured), therefore complications and related quality-of-life issues (such as impotence and incontinence) are multiplied by many years.[69]

Discussion of Primary and Secondary Prevention and Cost-Effectiveness

The main goal of prevention is not to save money but to spare people from avoidable misery and premature death. Primary and secondary prevention may indeed be cost-effective for some cancers, but this should be put into perspective when overall healthcare costs are being discussed. Part of the big picture that needs to be considered is that reducing or eliminating significant fatal diseases like cancer, heart disease, and strokes will make the population live longer, and at older ages is when disabling conditions such as osteoporosis and related fractures, dementia, and loss of vision and hearing become more common and healthcare costs are greatly increased. In nations with low mortality, prevention of fatal diseases without prevention of nonfatal, disabling conditions will increase healthcare costs in the long run.[70]

Though the cost-effectiveness, desirability, and safety of screening for some cancers is not always clear for the general population, it is usually much clearer for that segment of the population at high risk for certain cancers. For example, women with a hereditary mutation of the BRCA1 gene (about 1 in 600 women) have much higher percentages of developing breast cancer: 16 percent by age 40, 42 percent by age 45, 59 percent by age 50, 72 percent by age 55, and 80 percent by age 65. People with this mutation are more likely to get bilateral breast cancer and at a younger age, and it also raises the risk of colon cancer in both sexes by about 10 percent. Of 70-year-olds with this gene, 85 percent have had breast cancer, and 40-60 percent have ovarian cancer.[71] Though this paper is not focusing on those with high risk, clearly in cases such as these, earlier and more frequent cancer screenings are warranted, and sometimes more aggressive prevention that is not recommended for the general population, such as the drugs tamoxifen or raloxifene for breast cancer prevention (tamoxifen has been shown to reduce breast cancer occurrence in high-risk women, but with a potential for serious side effects, so a large clinical trial is underway comparing it to raloxifene, another SERM drug currently used for osteoporosis).

The problem in hereditary cancers is that there are not yet simple, inexpensive tests for determining who carries these mutations, and even if there were, there is often no current direct treatment, and there are other issues to consider. The most common ways of determining genetic risk are through examining family medical histories and from the patient herself, such as if a woman is diagnosed with breast cancer at a young age. DNA analysis and gene sequencing is now available, but it is time-consuming and expensive. There are abbreviated tests that are cheaper and only examine parts of genes but still cost several hundred dollars. These tests are only given to people with a family medical history suggesting certain inherited cancers, and only if they agree to it after weighing the pros and cons. Genetic testing is not routine because while the benefit is that it could identify certain inherited mutations and thus increased risk and the chance for more diligent screening efforts, whether the results are conclusive or inconclusive the current disadvantages and ethical issues remain: increased anxiety, impact on future child-bearing, and possible discrimination in obtaining health insurance, life insurance, and employment. This is currently legal in most states, and can happen even if it is discovered only that someone underwent genetic testing, regardless of the results.

The state's cancer plans provide comprehensive goals and objectives for promoting awareness and education about cancer, increasing prevention and screening efforts, and improving treatment and access to services. The Texas Cancer Plan is a plan for cancer in general, and plans also exist for specific cancers such as colorectal, lung, and skin, as well as prevention of spit tobacco use. Besides goals relating to the disease and increasing education efforts, data and research needs are also addressed in the cancer plans.

The cancer data collection system described in Goal IV, Cancer Data and Planning, of the Texas Cancer Plan[72] would be very useful if and when it becomes fully operational. The lack of consistent and specific data on many aspects of cancer control, especially cost data, in Texas and even nationwide, became very apparent during the course of this study. Having the various cancer-related entities cooperating and

utilizing a centralized data collection system that would be available to researchers and others would help the individual organizations' efforts as well as help policymakers to make decisions using more accurate and up-to-date information. If the strategies outlined in these plans are followed and supported with sufficient funding, the lives of many Texans will be improved. It cannot be guaranteed that these initiatives would save the state money. However, with well-designed primary and secondary prevention initiatives, the economic and social costs of cancer morbidity and premature mortality would be reduced.

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